DISSERTATION ON

Evaluation of transbronchial lung biopsy as diagnostic procedure in patients with suspected diffuse parenchymal lung disease

Submitted for

M.D., DEGREE EXAMINATION

Branch-XVII

TUBERCULOSIS & RESPIRATORY DISEASES

INSTITUTE OF THORACIC MEDICINE

Madras medical college & Govt. General Hospital

Chennai-600003

MARCH 2009

The Tamilnadu Dr. M.G.R.Medical University

Chennai 600032

March 2010

CERTIFICATE

This is to certify that the dissertation on **"EVALUATION OF TRANSBRONCHIAL LUNG BIOPSY AS DIAGNOSTIC PROCEDURE IN PATIENTS WITH SUSPECTED DIFFUSE PARENCHYMAL LUNG DISEASE"** is a record of research work done by **Dr.P.DURAIKANNAN** in partial fulfillment for M.D.BRANCH- XVII (T.B. and Respiratory Diseases) Examination of The Tamilnadu Dr. M.G.R.Medical University to be held in February 2010. The period of study is from March 2009 to october 2009.

Prof.Dr.N.Meenakshi, M.D, DTCD,

Director,

Institute of thoracic medicine, Chetpet,

Madras Medical college,

Chennai.

Prof. Dr.J.Mohanasundaram, M.D. Ph.D.,

Dean

Madras medical college & Govt. General Hospital

Chennai-600003.

DECLARATION

I hereby declare that the dissertation entitled **"EVALUATION OF TRANSBRONCHIAL LUNG BIOPSY AS DIAGNOSTIC PROCEDURE IN PATIENTS WITH SUSPECTED DIFFUSE PARENCHYMAL LUNG DISEASE"** submitted for the Degree of Doctor of Medicine in M.D., DEGREE EXAMINATION

Branch-XVII TUBERCULOSIS & RESPIRATORY DISEASES is my original work and the dissertation has not formed the basis for the award of any degree, diploma, associate ship, fellowship or similar other titles. It had not been submitted to any other university or Institution for the award of any degree or diploma.

Place: Chennai **(DR.P.Duraikannan)**

Date:

ACKNOWLEDGEMENT

I Would like to thank **DR. J.Mohanasundaram, MD** Dean, Madras Medical College & Govt. General Hospital for giving me permission to conduct the study in this institution.

I am deeply indebted to **Prof.DR.N.Meenakshi M.D,DTCD** Director, Institute of Thoracic Medicine, Chennai for her guidance and constant inspiration throughout my dissertation work. Words are few to express my gratitude to her for sparing her precious time and energy in trying to bring out the best in me.

I thank Additional professor **Dr.D.Ranganthan , M.D.,D.N.B.,** for his constant encouragement through out the post graduate course.

I am very grateful to **Dr. A.Chithrakumar, M.D.,** Associate professor, department of thoracic medicine, chetpet, Chennai and all assistant professors at our Thoracic Department for providing valuable guidance and timely advice.

I would like to express my sincere thanks and heartfelt gratitude to **Dr.Sridhar,M.D.,** Associate professor, I shall always cherish in my

heart for his constant encouragement, valuable guidance and relentless support throughout my postgraduate course.

I would also like to thank Dr**.Sundaram M.D,** Director ,Department of pathology, Government General hospital, Chennai for his immense help.

I would also like to thank **Prof. DR. R.Porkodi M.D, DM**, Director, Department of Rheumatology, Government General hospital, Chennai for her immense help.

Last but not the least, I thank all the patients who had participated in the study.

CONTENTS

INTRODUCTION

Diffuse parenchymal lung disease is a term given to a heterogeneous group of clinical entities that share the following features: dyspnea as the main symptom; hypoxemia; restrictive Ventilatory defect pattern in pulmonary function tests; and the presence of reticular, nodular, reticulonodular, or ground glass-appearing infiltrates on chest roentgenogram. However, "interstitial lung disease" is a misnomer, because this condition affects not only the interstitium but also the alveolar space and sometimes the airways. So the term diffuse parenchymal lung disease (DPLD) is more appropriate[1].

Under the heading of diffuse parenchymal lung disease, there are diverse aetiologies' that lead to similar histologic patterns[2]. These patterns are the main determinants of the clinical outcome of the patients and are also important in the differential diagnosis, mainly from other diseases that also affect interstitial compartment of the lungs.

Diffuse Parenchymal Lung disease is the fourth most common disease of the lungs, following chronic obstructive lung disease, asthma, and lung cancer[3]. Patients with diffuse interstitial lung diseases (DPLD) are challenging to treat. Many patients with DPLD have inadequate

information about the disease process, an imprecise diagnosis, unsatisfactory treatment or unacceptable side effects associated with therapy, and poorly controlled symptoms of progressive illness.

Establishing an accurate diagnosis is necessary so that the patient and his/ her family can be provided with reasonable expectations about prognosis and outcome from therapy.

Lung biopsy is required to establish the aetiology and stage of interstitial lung disease (DPLD). Lung biopsy is indicated for the following purposes[4]:

- To provide a specific diagnosis. This is especially desirable in a patient with atypical features (age <50 years, fever, weight loss, haemoptysis, signs of vasculitis); a progressive course; a normal, atypical, or rapidly changing chest radiograph or high resolution CT scan; unexplained extra pulmonary manifestations; or pulmonary vascular disease of unclear origin.

- To assess disease activity

- To exclude neoplastic and infectious processes that occasionally mimic chronic, progressive interstitial disease

- To identify a more treatable process than originally suspected

- To make a definitive diagnosis and predict prognosis before proceeding with therapies which may have serious side effects

Lung tissue is obtained via fiberoptic bronchoscopy with transbronchial biopsy, open thoracotomy, or video-assisted thoracoscopic lung surgery (VATS). All are subject to sampling error because the processes are often patchy and the sample sizes may be small[5].

Open lung biopsy (OLB) is considered the best method for diagnosing parenchymal lung disease. Nevertheless, despite recent advances in surgical techniques (ie, thoracoscopy), it is still considered an invasive procedure requiring general anaesthesia and is associated with substantial morbidity and mortality[6]

Open or thoracoscopic lung biopsy is appropriate when investigating diffuse disease in which either transbronchial lung biopsy has failed to establish the diagnosis or the clinical features suggest from the outset that a larger piece of tissue might be required.

Transbronchial lung biopsy — Fiberoptic bronchoscopy with transbronchial lung biopsy is often the initial procedure of choice, especially when sarcoidosis, lymphangitic carcinomatosis, eosinophilic

pneumonia, Good pasture's syndrome, or infection is suspected. TBLB via flexible bronchoscopy is a safe procedure with a low rate of complications[7]. Transbronchial biopsy can be performed at the same time as BAL and adds only a slight additional risk of bleeding and pneumothorax. For example, the combination of BAL, transbronchial lung biopsy, and transbronchial mediastinal lymph node aspiration has

proved to be very sensitive for the diagnosis of sarcoidosis, as demonstrated by Leonard and colleagues in 13 patients with suspected sarcoidosis; the combination provided a sensitivity of 100%.

Although an argument can be made for the 'blind' use of corticosteroid therapy in such situations, in that the prognosis of many such diffuse lung diseases is related more closely to response to steroids than to histological appearance, it is nevertheless standard practice to obtain tissue in these circumstances, a procedure likely to put the diagnosis on a firm footing and that should at the very least avoid the unusual but potentially disastrous confusion of sarcoidosis with miliary tuberculosis

AIM AND OBJECTIVE

To determine the Role of Transbronchial lung Biopsy as diagnostic procedure in Patients with diffuse parenchymal Lung Diseases.

REVIEW OF LITERATURE

The diffuse parenchymal lung diseases (DPLD) are a group of heterogeneous entities grouped together because of similar clinical, physiologic, radiologic and pathologic manifestations.

Under normal conditions, small numbers of interstitial macrophages, fibroblasts, and myofibroblasts (cellular components) reside within the interstitium. Other components (non-cellular) of the interstitium include the matrix proteins of the lung, consisting of a) collagen-related macromolecules and the b) non-collagenous proteins such as fibronectin and laminin. Interstitial fibrosis appears after injury occurs to the gas-exchanging units, increasing alveolar permeability, enabling the serum contents to enter the alveolar spaces.

Fibroblastic proliferation and excessive collagen deposition, the histologic hallmarks of interstitial lung disease, occur either as a *direct result* of the injury, as a result of an inflammatory cell response that releases pro-inflammatory and profibrotic cytokines, or *as a consequence* of the regenerative and reparative processes taking place at the epithelial and endothelial surfaces.

Over 150 separate entities are included in this classification with much confusion in the nomenclature[8]. The term “interstitial

lung disease" is a misnomer because these disorders have extensive alteration of

airways, lung parenchyma, blood vessels and pleura as well and "diffuse parenchymal lung disease (DPLD) is more appropriate. The diagnosis of individual disease is made after a careful consideration of clinical (thorough history and examination) features, radiology and pathology.

The clinician plays a central role in the evaluation of these entities because a comprehensive history and examination are central to the evaluation of these entities. The large number of individual entities necessitates a reductionist approach by grouping them according to clinical (etiologic, physiologic) or pathological features. Clinical sub-categorization enables easy evaluation; pathologic sub-classification predicts response.

Classification

1. I. Clinical classification:[9,10,11,12]

DPLD'S can be classified into seven major sub-groups etiologically

1. Idiopathic interstitial pneumonias
2. Collagen vascular-disease associated
3. Iatrogenic (drug/ radiation/ toxin) related

4. Inherited causes
5. Granulomatous diseases (known/ idiopathic)
6. Specific entities
7. Environmental/ occupational

II. Classification according to response:

1. Good response:

Eosinophilic pneumonia/ drug induced/ hypersensitivity pneumonitis/ vasculitis/organizing pneumonias/ Lymphoid interstitial pneumonia/Pulmonary alveolar protenosis/ sarcoidosis

2. **Sometimes times responsive**:

Diffuse alveolar damage/ Granulomatous lung disease / Diffuse alveolar haemorrhage.

3. Poorly responsive:

IPF/ Lymphangiomyomatosis/Pulmonary Langerhans – cell histiocytosis/Asbestosis

A good, detailed and structured history and clinical examination is necessary for the exclusion of connective tissue

disease, drug intake and occupational/ environmental exposure. The main aim is to differentiate from

1. IIP or non-IIP
2. IPF and non-IPF

However, it must be remembered that a confident clinical diagnosis of IPF has a very good specificity (97%) but poor sensitivity (62%). Use of HRCT improves the sensitivity to 78.5% (Raghu et al) with a specificity of 90% with expert evaluation; one third to a quarter of patients cannot be confidently diagnosed on clinical and radiologic grounds and will require a surgical lung biopsy. Clinical features and radiology perform even poorer for non-IPF IIP's (88 and 40% and 59% and 40%). The importance of the clinical evaluation, cannot, thus be overstressed.

I. Age

A. Paediatric ILD'S

i. Known aetiology

a. Hypersensitivity pneumonitis (and other environmental exposures)

b. Lipid storage diseases

c. Lipoid pneumonia

ILD mimics are important and need to be ruled out

d. Aspiration syndromes

e. Chronic infection (viral, bacterial, fungal, parasitic)

f. Bronchopulmonary dysplasia

ii. Unknown aetiology

a. Primary pulmonary: UIP/DIP/ NSIP/LIP/COP

IPH/ Lymphatic disorders/ alveolar microlithiasis/ PIE

b. Systemic disorders: CT-ILD/ Malignancies/ histiocytosis/ neurocutaneous syndromes/ sarcoidosis

Unique forms of DPLD in children include:

a. Persistent Tachypnea of infancy (PTI)/neuroendocrine cell hyperplasia of infancy (NEHI).

b. Follicular bronchitis/chronic bronchiolitis

c. Cellular interstitial pneumonitis of infancy

d. Acute idiopathic pulmonary haemorrhage of infancy (AIPHI)

e. Chronic pneumonitis of infancy

f. Idiopathic pulmonary fibrosis of infancy

g. Familial desquamative interstitial pneumonitis (DIP)

h. Surfactant protein abnormalities/congenital alveolar proteinosis

B. Age - 20-40 Years

Sarcoidosis

Connective tissue disease-associated ILD

Lymphangioleiomyomatosis

Pulmonary Langerhans cell histiocytosis

Inherited forms of ILD

Alveolar microlithiasis

C. <u>Age >50 Years</u>

IPF – approx 2/3 of pts are >60 years old at time of diagnosis

II. Sex

Certain ILD'S preferentially affect one gender

A. Male

a. Occupational ILD'S

b. PLCH

c. RB-ILD

d. CT-ILD related to rheumatoid arthritis

e. Idiopathic pulmonary fibrosis

B.Women

a. Connective tissue related ILD

b. Lymphangioleiomyomatosis (pre-menopausal females)

c. Hermansky-Pudlak syndrome

III. Depending on the mode of presentation

A. Acute presentation (days to weeks)

1. Acute idiopathic interstitial pneumonia

2. Accelerated presentation of UIP (Hamman-Rich syndrome)

3. Eosinophilic pneumonia

4. Hypersensitivity pneumonitis

5. Diffuse alveolar haemorrhage

6. Drug related ILD'S/ Toxic gases, fume related BOP

7. COP

8. Syndromic presentations of sarcoidosis (Lofgren and Heefort's). In acute ILD'S, great care is required to rule out infections and congestive cardiac failure.

B. Sub-acute presentation (weeks to months)

1. Sarcoidosis
2. Drug induced ILD
3. COP
4. CT-ILD

C. Chronic presentation (months to years)

1. IPF
2. CT-ILD
3. Chronic hypersensitivity pneumonitis
4. Pneumoconiosis (silicosis/ asbestosis)

Episodic DPLD'S

1. Eosinophilic pneumonia
2. Vasculitis
3. Alveolar haemorrhage

4. Hypersensitivity pneumonitis

5. Cryptogenic organising pneumonia

IDIOPATHIC INTERSTITIAL PNEUMONIA

Liebow, in 1975, classified idiopathic interstitial pneumonias (IIP) according to the histopathologic patterns. Since then, there has been considerable change in the understanding of interstitial lung diseases that led to a significant change in this classification system. Recently, Katzenstein and co-workers have suggested a classification that included not only chronic interstitial pneumonia (usual interstitial pneumonia - UIP and desquamative interstitial pneumonia-DIP), but also acute interstitial pneumonia (AIP) and Non specific interstitial pneumonia (NSIP) Travis and Colby have agreed upon Katzenstein classification but also have accepted bronchiolitis obliterans organizing pneumonia (BOOP) as a pattern of IIP.

HISTOLOGICAL AND CLINICAL CLASSIFICATION OF IDIOPATHIC INTERSTITIAL PNEUMONIAS

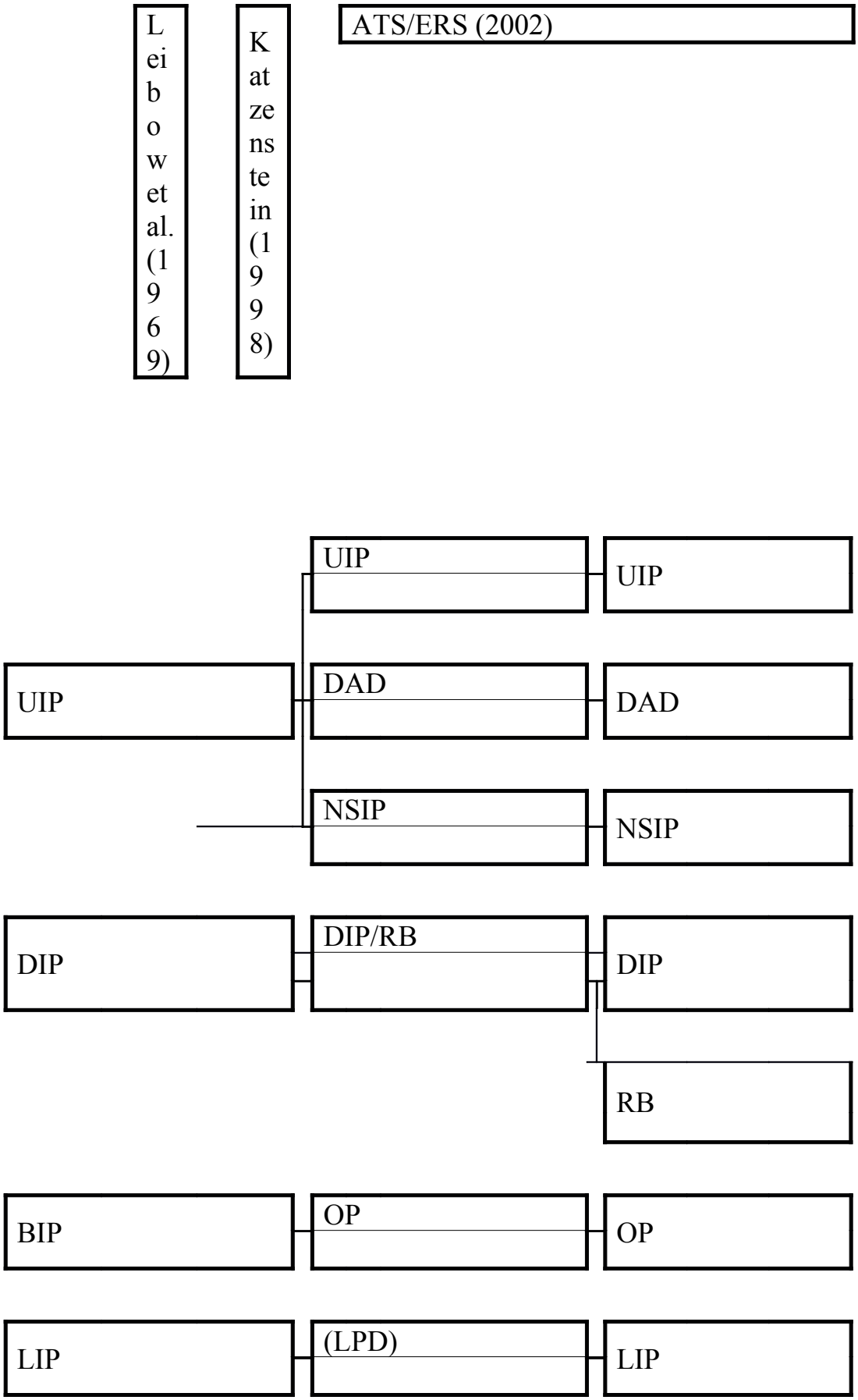
HISTOLOGICAL PATTERNS	Clinical, Radiological, Pathological diagnoses
Usual interstitial pneumonia	Idiopathic pulmonary fibrosis/cryptogenic fibrosing alveolitis
Nonspecific interstitial pneumonia	Nonspecific interstitial pneumonia (provisional)
Organizing pneumonia	Cryptogenic organizing pneumonia^{+}
Diffuse alveolar damage	Acute interstitial pneumonia
Respiratory bronchiolitis	Respiratory bronchiolitis interstitial lung disease
Desquamative interstitial pneumonia	Desquamative interstitial pneumonia
Lymphocytic interstitial pneumonia	Lymphocytic interstitial pneumonia

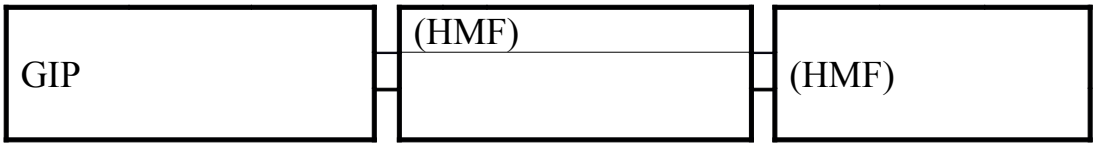
Unclassifiable interstitial pneumonia: some cases are unclassifiable for a variety of reasons.

This group represents a heterogeneous group with poorly characterized clinical and radiological features that need further study.

COP is the preferred term, but is synonymous with idiopathic bronchiolitis obliterans organizing pneumonia.

Development of the (histologic) idiopathic interstitial pneumonia classification[13,14,15]


Leibowet al. (1969)
Katzenstein (1998)
ATS/ERS (2002)
UIP
UIP
UIP
DAD
DAD
NSIP
NSIP
DIP
DIP/RB
DIP
RB
BIP
OP
OP
LIP
(LPD)
LIP



UIP=usual interstitial pneumonia; DAD=diffuse alveolar damage; NSIP=non-specific interstitial pneumonia; DIP=desquamative interstitial pneumonia; RB=respiratory bronchiolitis; BIP=bronchiolitis obliterans interstitial pneumonia; OP=organizing pneumonia; LIP=lymphoid interstitial pneumonia; LPD=lympho proliferative disease (not considered a diffuse lung disease); GIP=gaint cell interstitial pneumonia ; HMF=heavy metal fibrosis, no longer grouped with diffuse lung disease.

Lymphoid interstitial pneumonia was originally included in this category, then excluded, then included again.

Collagen vascular diseases are a group of diseases with specific autoimmune characteristics that affect several organs including the lungs.

Intrathoracic manifestations are frequent and may be asymptomatic or symptomatic, with varied degrees of severity. The pattern and frequency of the Intrathoracic involvement depend on the specific type of collagen vascular disease and may include one or more pulmonary compartments

such as alveolus, interstitium, vessels, lymphatic tissue, airways and pleura[20].

The most frequent pulmonary manifestations are diffuse interstitial pneumonias and pulmonary hypertension which as a whole represent the main causes of mortality and morbidity in these patients . It is important to note that pulmonary abnormalities in patients with collagen vascular disease may be due not only to the underlying disease, but also result from its treatment, and include drug reaction and infection by bacteria or opportunistic organisms, such as Pneumocystis jiroveci, and atypical mycobacteria as a result of immunosuppression.

The collagen vascular diseases that most commonly result in interstitial lung disease are rheumatoid arthritis, progressive systemic sclerosis, systemic lupus erythematosus, dermatopolymyositis, mixed connective tissue disease and Sjögren syndrome.

Interstitial pneumonias represent the most common Intrathoracic manifestations of collagen vascular disease . Collagen vascular diseases may be associated with virtually all patterns of diffuse interstitial pneumonia and may progress to pulmonary fibrosis . The histological

classification is similar to that of idiopathic interstitial pneumonias including: *a) patterns of chronic progression* - usual interstitial pneumonia, non-specific interstitial pneumonia and lymphocytic interstitial pneumonia; *b) pattern of sub acute progression* - organizing

pneumonia (also known as bronchiolitis obliterans organizing pneumonia —BOOP); *c) pattern of acute progression of pulmonary injury* - diffuse alveolar damage.

High-resolution CT manifestations of interstitial pneumonias in patients with collagen vascular diseases also are similar to the ones described for patients with idiopathic disease. Collagen vascular diseases most frequently associated with interstitial pneumonia are:[21,22] rheumatoid arthritis, progressive systemic sclerosis (scleroderma) and dermatopolymyositis.

In general, non-specific interstitial pneumonia is the most common pattern of interstitial pneumonia in patients with collagen vascular diseases. In patients with rheumatoid arthritis[23,24], however, it seems that the pattern of usual interstitial pneumonia is the most frequent one. On the other hand, lymphocytic interstitial pneumonia, although rare, is most common in patients with Sjögren's syndrome, while the diffuse alveolar damage pattern is more frequent in patients with dermatopolymyositis and systemic lupus erythematosus.

In general, chronic progressive interstitial pneumonias in collagen vascular diseases have a better prognosis than those of idiopathic nature, with a better five year survival rate. However, cases of unfavourable progression in patients with collagen vascular disease and interstitial

pulmonary involvement with no response to the therapy are not infrequent. Similarly to the idiopathic form of disease, the non-specific interstitial pneumonia pattern in collagen vascular disease has a better prognosis than the pattern of usual interstitial pneumonia.

The concomitant presence of more than one pattern of interstitial pneumonia, particularly the association between non-specific interstitial pneumonia and organizing pneumonia (BOOP) is not rare in collagen vascular disease, and is most common in patients with dermatopolymyositis and mixed connective tissue disease. Generally, the pattern of diffuse alveolar damage is associated with poor prognosis, both in patients with idiopathic disease and patients with collagen vascular disease .

Interstitial pneumonias may precede the clinical onset of the collagen vascular disease for a period of three months up to five years, usually with a pattern of non-specific interstitial pneumonia or acutely with a pattern of diffuse alveolar damage. Patients with collagen vascular disease, especially rheumatoid arthritis, scleroderma and dermatopolymyositis, may progress with acute exacerbation of fibrotic interstitial pneumonia.

Most frequently, acute pulmonary injury manifests histologically as diffuse alveolar damage superimposed on underlying pulmonary

fibrosis (generally usual interstitial pneumonia or non-specific interstitial pneumonia patterns). HRCT findings of acute exacerbation of chronic progressive interstitial pneumonia in patients with collagen vascular disease consist in diffuse areas of ground-glass attenuation, with or without associated smooth inter- and intralobular lines resulting in a *crazy paving* pattern associated with signs of fibrosis from the pre-existing interstitial pneumonia (distortion of pulmonary architecture, traction bronchiectasis, reticulation and honeycombing).

Areas of focal or bilateral dependent consolidation may be present. The main differential diagnosis for ground-glass attenuation at HRCT in patients with collagen vascular disease and fibrotic interstitial pneumonia includes opportunistic infections (particularly by *Pneumocystis*) and drug-induced lung disease. Consolidation may be due to organizing pneumonia or an infectious process (by bacteria, mycobacteria or fungi). Sarcoidosis is a multisystem granulomatous disorder of unknown aetiology most commonly affecting young adults and presenting most frequently with bilateral hilar lymphadenopathy, pulmonary infiltration and skin or eye lesions.

The diagnosis is established most securely when clinic radiographic findings are supported by histological evidence of

widespread noncaseating epithelioid granulomas in more than one organ or a positive Kveim–Siltzbach skin test. Immunological features are depression of delayed-type hypersensitivity, suggesting impaired cell-mediated immunity, and raised or abnormal Immunoglobulin's.

Many types of abnormality may be seen on the chest film and these may be classified as follows:[25]

1 disseminated miliary lesions

2 disseminated nodular lesions

3 linear type of infiltration extending fan-wise from the hilum;

4 diffuse and confluent patchy shadows;

5 diffuse fibrosis

6 diffuse fibrosis with cavitation

7 diffuse ground-glass shadowing

8 changes similar to chronic tuberculosis as regards location and distribution;

9 bilateral confluent massive opacities resembling areas of pneumonia;

10 atelectasis.

Transbronchial biopsy of lung and bronchial wall via the flexible fiberoptic bronchoscope is the procedure of choice in the diagnosis of diffuse pulmonary abnormality of probable sarcoid aetiology and is employed especially if there are cogent reasons for securing a diagnosis earlier than can be expected from the Kveim test. A minimum of four lung biopsies by this method optimizes the chances of securing a diagnosis.

Pulmonary alveolar microlithiasis is a disease that is often familial and characterized by a radiographic appearance of very fine, sand-like mottling uniformly distributed through both lungs. This mottling represents an extensive. Intra-alveolar deposit of calcium-containing bodies. Despite extensive radiographic changes, symptoms at the time of discovery are often minimal or absent, but later there is gradual progression to respiratory failure and cor Pulmonale. Although not usually required, bronchoalveolar lavage or biopsy can confirm the diagnosis. Biopsy shows calcified spherules filling alveolar spaces.

Hypersensitivity pneumonitis (HP), or extrinsic allergic alveolitis, is a spectrum of interstitial, alveolar, and bronchiolar lung diseases resulting from immunologically induced inflammation in response to inhalation of a wide variety of different materials that are usually organic or low-molecular weight chemical antigens (or haptens) that may lead to irreversible lung damage.

A lung biopsy specimen is generally required when there is significant doubt about the diagnosis. Transbronchial lung biopsies often do not provide sufficient material to fully establish the presence and interrelationships of granulomas, bronchiolitis, and interstitial inflammation, so either open or thoroscopically obtained lung biopsies may be necessary.

MATERIALS AND METHODS

This prospective study was organized in department of Thoracic medicine in association with department of Rheumatology, Government General Hospital,chennai. Subjects were recruited from the thoracic and Rheumatology outpatient clinic of our hospital. Approval from Medical Ethical Committee has been obtained

The study period extended from February 2009 to October 2009

DESIGN OF THE STUDY:

Prospective study.

INCLUSION CRITERIA

1. Radiologically suspected cases of DPLD.
2. Age > 12 years.
3. Sex- Both genders.

Presence of respiratory signs and symptoms suggestive of DPLD

5. willing for study with informed consent

EXCLUSION CRITERIA

Uncorrectable hypoxemia/hypercapnia

Unstable myocardium

Uncorrectable bleeding tendency

Tracheal stenosis

Poorly controlled asthma

7. Age less than 12

8. Patients with elevated renal parameters

9. Uncooperative patient

METHODOLOGY

Patients who were fulfilling the inclusion criteria were included for the study after obtaining the written informed consent.They were subjected to the following investigation

1. THOROUGH CLINICAL EVALUATION
2. HRCT CHEST
3. PULMONARY FUNCTION TEST
4. BRONCHOSCOPY AND TBLB

THOROUGH CLINICAL EVALUATION

In essence, without proper medical history all diffuse parenchymal lung diseases are of unknown cause. For an accurate diagnosis, there is no substitute for complete clinical evaluation. This should be considered as the key diagnostic steps in the evaluation of patient who has DPLD.

Thorough history elicitation with comprehensive evaluation of the chief complaint and comprehensive review of multiple systems were done.

Medical history was taken with special reference to previous cardiopulmonary disease, cough, exertional dyspnea, sputum, chest pain and risk factors for pulmonary disease, such as smoking.

Then followed by exhaustive review of past medical, social, family and occupational histories with an exploration of all potential environmental exposures were done. The clues that surface during this evaluation help to narrow the broad differential diagnosis to few possible disorders as per ATS recommendation.

HRCT CHEST

The patients were then subjected to the High-resolution computed tomography (HRCT) in the supine position, holding breath at deep inspiration, without contrast medium. Prone sections were taken when posterior images obtained on supine sections were suspected of having artefacts due to gravity dependent perfusion. The added value of HRCT scanning in DPLD depends upon its ability to increase confidence of a specific diagnosis by characterisation and profusion of lesion on representative anatomical level, to alter patient management and if possible, to influence the outcome

PULMONARY FUNCTION TESTS

After completing the physical examination and HRCT of those who have fulfilled criteria, were subjected to pulmonary function test.

The various manoeuvres of spirometry were explained and practically demonstrated to them.

PFT was deferred to those persons who were suspected of having symptoms of respiratory tract infection. A course of antibiotics were given to them and asked to come for the next session for the completion of PFT.

BRONCHOSCOPY AND TRANSBRONCHIAL LUNG BIOPSY

After above procedures, patient was assessed for bronchoscopy and transbronchial lung biopsy. Consent for bronchoscopy and biopsy were obtained. Thirty two patients were studied. Patients were selected on the basis of a chest radiography compatible with diffuse lung disease without prior tissue diagnosis.

Under topical anaesthesia transbronchial lung biopsy and bronchoalveolar lavage was carried through fiberoptic bronchoscope at same setting. All patients were given glycopyrrolate(.2mg) as premedication. Fluoroscopy was not employed. For all patients BAL and TBLB was done in same setting. BAL was done in middle lobe or lingula. TBLB were obtained from the lower lobe segments on the side of greatest involvement, if any, or from the right lower lobe if disease was distributed equally by lung imaging. Four to six biopsies taken at the

same time. In this procedure, the upper lobes, middle lobe and lingula were avoided because, without parietal pleural pain as a warning, the major fissure may be transversed, with resultant pneumothorax.

Samples were sent for cytology, cell count, microbiological study and histopathologic analysis in government general hospital. For all patient chest x ray was taken after the procedure, to rule out any procedure related pneumothorax. Patient were under medical supervision to pick up any procedure related complications.

Transbronchial lung biopsy[26,27]

Transbronchial (sometimes referred to as 'bronchoscopic') lung biopsies are made beyond the limits of direct vision and may be conveniently carried out under fluoroscopic control using a C-arm or other suitable device, although some bronchoscopist have been content to work without any such assistance. Where there is diffuse disease that is bilateral, the tip of a larger Channel bronchoscope may be wedged into a laterally placed segmental bronchus in either lower lobe, as these usually accept the forceps comfortably. At this point, 5mL of1: 20000 epinephrine solution is injected into the chosen segmental orifice in the belief that this diminishes the likelihood of serious bleeding .The largest possible toothed biopsy forceps are then passed through the same

segmental opening, while the end of the bronchoscope remains wedged into that segment, the shaft of the bronchoscope nearest the patient being held by the assistant, with gentle inward pressure, so that the bronchoscopist is free to advance the forceps. If the forceps reach the extreme periphery of the lung, Pleuritic pain may be felt and the forceps are withdrawn a few centimetres to reduce the chance of pneumothorax.

If the forceps are arrested early in their journey, another basal segment is tried instead, as too proximal a biopsy runs a small risk of damaging a larger blood vessel. When the forceps appear to be well situated towards the lung periphery, the patient is asked to ‘take a deep breath in and hold it’ and the assistant is given the instruction ‘open’. and they are then pushed gently forwards until resistance is felt, whereupon the patient is asked to ‘let all your air out’ and the assistant is given the instruction ‘close’ when expiration is seen to be complete. The forceps are then firmly withdrawn. An elastic tug followed by a feeling of ‘give’ is sensed and lung tissue may be seen to be pulled and to recoil back into place on the screen. This is usually a sign that a satisfactory biopsy has been obtained. The biopsy material is then placed in fixative(formalin) for histopathology or normal saline for microbiology.

Transbronchial biopsy: mechanism whereby acinar tissue may be obtained

RESULTS

In our study 50 patients were screened for Diffuse Parenchymal Lung Diseases. Out of which 32 patients were taken up for the study after satisfying eligible criteria. Remaining patients were excluded from the study group based on exclusion criteria.

AGE

In our study population age group ranges from 14-70 years.

Table 1

Age Group (Years)	No of Patients	Percentage (%)
<20	2	
20-40	11	
40-60	17	
>60		

2

6.25

34.37

53.12

6.25

TOTAL

32

100

Maximum number of patients presented between the ages of 40-60 years. The mean age distribution found in our study is 42 year.

SEX

Table 2

SEX	No of Patients	Percentage (%)
Male	13	40.62
Female	19	59.37
Total	32	100

The selected patients consisted of 59.37% Females and 40.62% males.

DISEASE(Etiologic) CLASSIFICATION:

In my study patients are grouped according to aetiology through clinical and radiological grounds

(Table 3)

DISEASE	NO OF PATIENTS	PERCENTAGE
KNOWN ETIOGY	15	46.875
UNKNOWN ETILOGY	10	31.25
GRANULAMATOUS LUNG DISEASE	6	18.75
RARER FORM	1	3.125

TOTAL	**32**	**100**

As the above pie diagram shows in my study most predominant HRCT finding is mixed pattern.

DISEASE CLASSIFICATION[28]:

DPLD was subdivided into four subgroups according to aetilology.1.DPLD of unknown cause which includes IIP, 2.DPLD associated with identifiable cause, such as environmental exposure or systemic illness such as collagen vascular diseases,3.granulamatous diseases such as sarcoidosis, hypersensitivity pneumonitis, and tuberculosis, 4.few rarer form of DPLD such as LCH , LAM,and PAM.

Out of 32 cases 15 cases are associated with known causes,10 cases are of unknown etiology classified as idiopathic interstitial pneumonia, six cases are granulomatous lung disease and 1 cases are classified in rarer form of DPLD.

In 15 cases of known etiology group, 4 cases are known rheumatoid arthritis patient,1 case was SLE, dermatomyositis 1 case, 3 cases are systemic sclerosis, 2 cases are overlap syndrome,1 case was drug induced DPLD(methotrexate) and 2 cases was Lymphangitis carcinomatosis.

Out of 10 cases of IIP 5 cases are smoking related, 5 cases with unknown etiology.

In 6 cases of granulomatous lung disease 3 cases are suspected sarcoidosis and 3 are suspected tuberculosis(pre biopsy diagnosis).

In rarer form of DPLD one case was pulmonary alveolar microlithiasis.

CLINICAL FEATURE:

The predominant symptom found in majority of the study cases are Exertional dyspnoea(88.89%), followed by cough(50%) and chest pain(25%) fever 12(%)cases. Bibasilar crackles heard in 16 cases out of 32 cases.

Extra pulmonary symptoms are Dyspepsia, Dysphagia, Reynaud's phenomenon, inflammatory arthritis, subcutaneous nodules, Sicca syndrome, Skin changes like rash, discolouration and thickening, proximal muscle weakness, etc . These above-mentioned symptoms present concomitantly in our cases and these symptoms have either preceded or accompanied with respiratory illness.

Age group versus clinical diagnosis

(Table 4)

Age Group	Unknown Etilogy	Known Etilogy	Granulamatous Lung Disease	Rarer Form
<20	0	0	1	1
20-40	3	7	2	0
40-60	6	7	3	
>60	1	1	0	0
Total	10	15	6	1

AGE GROUP VERSUS TRANSBRONCHIAL LUNG BIOPSY (Table 5)

Age group	Nsip	Sarcoi-dosis	Tb	Pam	Lymphangitis carcinomatosa	Not contribuat-ory	Total
<20	0	0	1	1	0	0	2
20-40	4	0	0	0	0	7	11
40-60	6	1	0	0	1	7	15
>60	0	0	0	0	0	2	2
Total	10	1	1	1	1	16	30

DISCUSSION

Diffuse parenchymal lung disesase (DPLD) is a term given to a heterogeneous group of clinical entities that share the following features: dyspnea as the main symptom; hypoxemia; restrictive Ventilatory defect pattern in pulmonary function tests; and the presence of reticular, nodular, reticulonodular, or ground glass-appearing infiltrates on chest roentgenogram.

Under the heading of diffuse parenchymal lung disease, there are diverse aetiologies' that lead to similar histologic patterns. These patterns are the main determinants of the clinical outcome of the patients and are also important in the differential diagnosis, mainly from other diseases that also affect interstitial compartment of the lungs.

Many patients with DPLD have inadequate information about the disease process, an imprecise diagnosis, unsatisfactory treatment or unacceptable side effects associated with therapy, and poorly controlled symptoms of progressive illness. Establishing an accurate diagnosis is necessary for clinician to plan appropriate management as well as the patient and his/her family can be provided with reasonable expectations about prognosis and outcome from therapy.

The diagnosis of individual disease is made after a careful consideration of clinical features(thorough history and examination), radiology and Histopathological examination

In my study DPLD was subdivided into IIP,DPLD of known causes, granulomatous disease and rarer form of DPLD such as LCH , LAM,and PAM.

Out of 32 cases 15 cases are of known causes such as collagen vascular disease ,drug induced DPLD(methotrexate) and Lymphangitis carcinomatosis,10 cases are classified as idiopathic interstitial pneumonia, six cases are granulomatous lung disease and 1 cases are classified in rarer form. In 12 cases of collagen vascular lung disease 4 cases are known rheumatoid arthritis patient,1 case was SLE,dermatomyositis 1 case, 3 cases are systemic sclerosis, 2 cases are overlap syndrome.

Out of 10 cases of IIP 5 cases are smoking related, 5 cases with unknown etiology.

In 6 cases of granulomatous lung disease 3 cases are suspected sarcoidosis and 3 are suspected tuberculosis(pre biopsy diagnosis).

In rarer form 1 case was pulmonary alveolar microlithiasis, Our study principally focuses mainly on diagnostic yield of transbronchial lung biopsy in assessing the prognosis and excluding the other diseases.

Out of 32 cases .in my study 59.37 %(19) were female and 40.62%(13) were male. Maximum number of patients presented between the ages of 40-60 years. The mean age distribution found in our study is42 year.

Most cases presented with mixed pattern in HRCT. Out of 32 cases for 14 cases we got specific diagnosis which is around 43.75%. among which NSIP in 10 ,tuberculosis in 1,sarcoidosis in 1,pulmonary alveolar microlithiasis in 1,lymphanjitis carcinomatosis in 1,for 16 cases we couldn't get specific diagnosis. And for 2 cases the biopsy sample reported as inadequate.

Out of 32 cases who had undergone TBLB one case developed pneumothorax after the procedure which did not require intercostal drainage.

In Ailani RK[29] et al study histopathologic diagnosis is obtained in 77%. Complications encounted were haemorrhage (23%), pneumothorax (3%), and post biopsy chest pain in (3%).

Comparing to above study in our study histopathological diagnosis is obtained in 43.75%.complication in one patient(3%) and none of the patient developed haemorrhage.

CONCLUSION

Transbronchial lung biopsy is a relatively safe method for diagnosing specific diffuse parenchymal lung disease and for obtaining histological pulmonary specimens which aids in excluding other etiologic causes of diffuse parenchymal lung disease.

We recommend use of this diagnostic procedure as a supplementary to HRCT and clinical examination. but more number of cases are needed to prove definitely acceptable outcomes so that the technique can be a part of diagnosing diffuse parenchymal lung disease.

We conclude that, to determine the prognosis and appropriate therapeutic intervention for the patient, accurate pathological diagnosis in conjugation with clinical and radiological finding is mandatory.

ABBREVIATION

ATS	American Thoracic Society
BAL	Bronchoalveolar Lavage
BIP	Bronchiolitis obliterans organising pneumonia
CVD	Collagen Vascular Disease
COP	Cryptogenic Organizing Pneumonia
DPLD	Diffuse parenchymal lung disease
DAD	Diffuse alveolar damage
DIP	Desquamative Interstitial Pneumonitis
GIP	Gaint Cell interstitial pneumonia
HRCT	High resolution contrast CT
ILD	Interstitial lung diseases
LIP	Lymphocytic Interstitial Pneumonitis
MCTD	Mixed Connective Tissue Disease
NSIP	Non-Specific Interstitial Pneumonitis
PFT	Pulmonary Function Test
PM/DM	Polymyositis/Dermatmyositis
RA	Rheumatoid Arthritis
RBILD	Respiratory Bronchiolitis Interstitial Lung Disease
SLE	Systemic Lupus Erythematosus
SS	Systemic Sclerosis
UIP	Usual interstitial pneumonia

BIBLIOGRAPHY

1) The Diagnosis, Assessment and Treatment of Diffuse Parenchymal Lung Disease in Adults. BRITISH THORACIC SOCIETY and STANDARDS OF CARE COMMITTEE *Thorax* 1999;54;S1-S28.

2) Ryu jh,Colby TV ,Hartman te.IPF: current concepts. Mayo clinic proc 1998;73:1085-1101.

3) Coultas DB,zumwalt. RE,black wc,et al.the epidemiology of interstitial lung diseases. Am journal of respiratory care medicine 1994:150;967-972.

4) Poletti, V, Chilosi, M, Olivieri, D. Diagnostic invasive procedures in diffuse infiltrative lung diseases. Respiration 2004; 71:107

5) Talmadge E King, Jr, MD Role of lung biopsy in the diagnosis of interstitial lung disease. Halkos, ME, Gal, AA, Kerendi, F, et al. Role of thoracic surgeons in the diagnosis of idiopathic interstitial lung disease. Ann Thorac Surg 2005; 79:2172.

6) The Role of Open Lung Biopsy in the Management and Outcome of Patients With Diffuse Lung Disease. Mordechai R Kramer MD, Neville Berkman MBBCh, Bella Mintz MD, Simon Godfrey MD, PhD, Milton Saute MD[D]and Gail Amir MBBCH The Annals of Thoracic SurgeryVolume 65, Issue 1, January 1998, Pages 198-202.

7) The safety of outpatient transbronchial biopsy. M Ahmad, D R Livingston, J A Golish, A C Mehta and H P Wiedemann *Chest* 1986;90;403-405.

8) Walters EH, du Bois R, eds. *Immunology and management of interstitial lung diseases*. London: Chapman & Hall, 1995. *Thorax* 1999;**54** (Suppl 1):S15–S30.

9) Allen JN,Davis WB. Eosinophilic lung diseases. *Am J Respir Crit Care Med* 1994;**150**:1423–38.

10) Davison AG, Heard BE, McAllister WAC, *et al*.Cryptogenic organising pneumonitis.*Q J Med* 1983;**52**:382–94.

11) Fauci AS, Haynes BF, Katz P, *et al*. Wegener's granulomatosis: prospective clinical and therapeutic experience with 55 patients for 21 years. *Ann Intern Med* 1983;**98**:76–85.

12) White DA, Stover DE. Severe bleomycin induced pneumonitis. Clinical features and response to corticosteroids.*Chest* 1984;**86**:723–8.

13) American Thoracic Society/EuropeanRespiratory Society International. Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and theEuropean Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med* 165:277–304, 2002.

14) Katzenstein AL, Myers JL: Idiopathic pulmonary fibrosis: Clinical relevance of pathological classification. *Am J. Respir Crit Care Med* 157:1301–1315, 1998.

15) Liebow a .definition and classification of interstitial pneumonia in human pathology. Prog respire res 1975;8:1-33.

16) Katzenstein AL,Fiorelli Rf.NSIP: histologic features and clinical significance Am j surg pathology 1994;18:136-147.

17) Travis wd ,matsui k,moss j,et al .idiopathic NSIP prognostic significance of cellular and fibrosing patterns. Am j resp crit care 1998;138:1288-1295.

18) Nagai s,kitaichi m,itoh H,et al. Idiopathic NSIP comparision with idiopathic NSIP and BOOP eur respir jounal 1998;12:1010-1019

19) Katzenstein AL, Katzenstein and askins surgical pathology of non neoplastic lung disease .W.B saunders,Philadelphia:1997

20) [Interstitial pneumonia associated with collagen vascular diseases: histological findings, and cells in bronchoalveolar lavage fluid]. Nihon Kyobu Shikkan Gakkai Zasshi. 1995; 33 Suppl:258-63

21) Fiedorczyk M, Rojewska J, Kowal-Bielecka O, Sierakowski S. Interstitial lung disease related to systemic connective tissue diseases. *Przegl Lek*. 2005;62(12):1471-4. [Medline].

22) Jindal SK, Agarwal R. Autoimmunity and interstitial lung disease. *Curr Opin Pulm Med*. Sep;2005;11(5):438-46. [Medline].

23) Herzog CA, Miller RR, Hoidal JR. Bronchiolitis and rheumatoid arthritis. *Am Rev Respir Dis*. Nov;1981;124(5):636-9. [Medline].

24) Corrin B, Turner-Warwick M, Geddes DM, Brewerton DA. Bronchiolitis obliterans. A new form of rheumatoid lung?. *Chest*. Feb;1978;73(2):244. [Medline].

25) Transbronchial lung biopsy in pulmonarysarcoidosis. Is it an evaluable method in detection of disease activity? V Poletti, M Patelli, L Spiga, R Ferracini and V Manetto. Chest 1986;89;361-365, DOI 10.1378/chest.89.3.361

26) de Fenoyl O, Capron F, Lebeau B *et al.* Transbronchial biopsy without fluoroscopy: a five year experience in outpatients. *Thorax* 1989; 44: 956.

27) Hanson RR, Zavala DC, Rhodes ML *et al.* Transbronchial biopsy via flexible fiberoptic bronchoscope: results in 164 patients. *AmRev Respir Dis* 1976; 114: 67.

28) Fishman pulmonary disease and disorders.chapter 68 page no 1145

29) R.K.Ailani,R.K.Issac,S.P.Koyande and J.V.Mandke. Transbronchial biopsy in diffuse lung disease. Ind. J.tub;1993,40,199

30)

BIBLIOGRAPHY

1) The Diagnosis, Assessment and Treatment of Diffuse Parenchymal Lung Disease in Adults. BRITISH THORACIC SOCIETY and STANDARDS OF CARE COMMITTEE *Thorax* 1999;54;S1-S28.

2) Ryu jh,Colby TV ,Hartman te.IPF: current concepts. Mayo clinic proc 1998;73:1085-1101.

3) Coultas DB,zumwalt. RE,black wc,et al.the epidemiology of interstitial lung diseases. Am journal of respiratory care medicine 1994:150;967-972.

4) Poletti, V, Chilosi, M, Olivieri, D. Diagnostic invasive procedures in diffuse infiltrative lung diseases. Respiration 2004; 71:107

5) Talmadge E King, Jr, MD Role of lung biopsy in the diagnosis of interstitial lung disease. Halkos, ME, Gal, AA, Kerendi, F, et al. Role of thoracic surgeons in the diagnosis of idiopathic interstitial lung disease. Ann Thorac Surg 2005; 79:2172.

6) The Role of Open Lung Biopsy in the Management and Outcome of Patients With Diffuse Lung Disease. Mordechai R Kramer MD, Neville Berkman MBBCh, Bella Mintz MD, Simon Godfrey MD, PhD, Milton Saute MD[D]and Gail Amir MBBCH The Annals of Thoracic SurgeryVolume 65, Issue 1, January 1998, Pages 198-202.

7) The safety of outpatient transbronchial biopsy. M Ahmad, D R Livingston, J A Golish, A C Mehta and H P Wiedemann *Chest* 1986;90;403-405.

8) Walters EH, du Bois R, eds. *Immunology and management of interstitial lung diseases*. London: Chapman & Hall, 1995. *Thorax* 1999;**54** (Suppl 1):S15–S30.

9) Allen JN,Davis WB. Eosinophilic lung diseases. *Am J Respir Crit Care Med* 1994;**150**:1423–38.

10) Davison AG, Heard BE, McAllister WAC, *et al*.Cryptogenic organising pneumonitis.*Q J Med* 1983;**52**:382–94.

11) Fauci AS, Haynes BF, Katz P, *et al*. Wegener's granulomatosis: prospective clinical and therapeutic experience with 55 patients for 21 years. *Ann Intern Med* 1983;**98**:76–85.

12) White DA, Stover DE. Severe bleomycin induced pneumonitis. Clinical features and response to corticosteroids.*Chest* 1984;**86**:723–8.

13) American Thoracic Society/EuropeanRespiratory Society International. Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and theEuropean Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med* 165:277–304, 2002.

14) Katzenstein AL, Myers JL: Idiopathic pulmonary fibrosis: Clinical relevance of pathological classification. *Am J. Respir Crit Care Med* 157:1301–1315, 1998.

15) Liebow a .definition and classification of interstitial pneumonia in human pathology. Prog respire res 1975;8:1-33.

16) Katzenstein AL,Fiorelli Rf.NSIP: histologic features and clinical significance Am j surg pathology 1994;18:136-147.

17) Travis wd ,matsui k,moss j,et al .idiopathic NSIP prognostic significance of cellular and fibrosing patterns. Am j resp crit care 1998;138:1288-1295.

18) Nagai s,kitaichi m,itoh H,et al. Idiopathic NSIP comparision with idiopathic NSIP and BOOP eur respir jounal 1998;12:1010-1019

19) Katzenstein AL, Katzenstein and askins surgical pathology of non neoplastic lung disease .W.B saunders,Philadelphia:1997

20) [Interstitial pneumonia associated with collagen vascular diseases: histological findings, and cells in bronchoalveolar lavage fluid]. Nihon Kyobu Shikkan Gakkai Zasshi. 1995; 33 Suppl:258-63

21) Fiedorczyk M, Rojewska J, Kowal-Bielecka O, Sierakowski S. Interstitial lung disease related to systemic connective tissue diseases. *Przegl Lek*. 2005;62(12):1471-4. [Medline].

22) Jindal SK, Agarwal R. Autoimmunity and interstitial lung disease. *Curr Opin Pulm Med*. Sep;2005;11(5):438-46. [Medline].

23) Herzog CA, Miller RR, Hoidal JR. Bronchiolitis and rheumatoid arthritis. *Am Rev Respir Dis*. Nov;1981;124(5):636-9. [Medline].

24) Corrin B, Turner-Warwick M, Geddes DM, Brewerton DA. Bronchiolitis obliterans. A new form of rheumatoid lung?. *Chest*. Feb;1978;73(2):244. [Medline].

25) Transbronchial lung biopsy in pulmonarysarcoidosis. Is it an evaluable method in detection of disease activity? V Poletti, M Patelli, L Spiga, R Ferracini and V Manetto. Chest 1986;89;361-365, DOI 10.1378/chest.89.3.361

26) de Fenoyl O, Capron F, Lebeau B *et al.* Transbronchial biopsy without fluoroscopy: a five year experience in outpatients. *Thorax* 1989; 44: 956.

27) Hanson RR, Zavala DC, Rhodes ML *et al.* Transbronchial biopsy via flexible fiberoptic bronchoscope: results in 164 patients. *AmRev Respir Dis* 1976; 114: 67.

28) Fishman pulmonary disease and disorders.chapter 68 page no 1145

29) R.K.Ailani,R.K.Issac,S.P.Koyande and J.V.Mandke. Transbronchial biopsy in diffuse lung disease. Ind. J.tub;1993,40,199